

Attention: Dr Barbara Shane, Executive Secretary

NTP Office of Liason Policy and Review

Dear Dr Shane:

Background -- Dr Arthur Grollman (Stony Brook University) invited me to comment on the National Toxicology Program Draft Report on Aristolochic acid (AA) exposures in view of my long term interest in upper urothelial cancer associated with Balkan Endemic nephropathy. As noted in your draft Report (pp 57-64), it is likely that dietary ingestion of aristolochic acid plays a central etiologic role in Balkan endemic nephropathy and its associated upper urothelial cancer (UUT). Primary references summarizing observations in over 2000 patients with UUT may be found in my book, published in 2006. The book (ref 1) is written in Serbian with English summaries and I have published some of the main observations in international journals (ref 4). An earlier review of this subject in English by Petronic may be found in reference 2.

Specific comments:

P 58, line 1 – It is misleading to term BEN a “familial” disease as this designation suggests inheritance. BEN is indeed concentrated in certain households reflecting common exposure through ingestion of the same (contaminated) home baked bread. I recommend deleting the word “familial” in this sentence. You may also wish to note that some isolated (sporadic) cases of BEN and upper urothelial tumors (UUT) have been reported outside the areas designated as “endemic” villages.

P58, line 16-- As described in ref 1, there is a relationship between the prevalence of BEN and altitude of endemic villages. This well documented association may be relevant to the mechanism of exposure.

P58, line 24 -- I suggest deleting the word “severe” since patients with UUT come to surgery with severe, moderate, or mild renal dysfunction or no renal disease at all.

P58, line 25-26 – The sentence should be clarified by deleting the words “suggesting that botanical products containing”

Discussion -- The introductory paragraph limits the subsequent discussion of aristolochic acid induced urothelial cancer to patients treated with herbal medicines. Since your draft Report focuses on the carcinogenic properties of aristolochic acid, I suggest adding to the discussion a section on UUT associated with BEN. Evidence that patients with UUT have been exposed to aristolochic acid (ref 5) is very strong, based on the presence of aristolochic acid derived DNA adducts in renal and tumor tissue and a characteristic mutational “fingerprint” in the P-53 tumor suppressor gene.

The literature includes thousands of cases of BEN-associated UUT and relatively few reported cases of UUT associated with herbal remedies; thus much can be learned relevant to aristolochic acid carcinogenesis in humans by considering such studies when assembling your Report. References 1 and 2 (latter is in English) contains citations supporting the following statements:

- Since hemodialysis became available, the lifespan of patients with BEN was extended. As the latent period for induction of this tumor is long, many more were reported to have developed UUT.

- Sporadic cases of UUT in older patients (associated with mild or absent renal failure) is consistent with ingestion of low amounts of aristolochic acid over an extended period of time.
- The age when patients in endemic regions develop symptoms associated with UUT has steadily increased over the past 30 years (ref 4), suggesting that the level of exposure to aristolochic acid is diminishing.
- UUT in BEN include low grade and high grade (locally invasive) cancers. The fraction of high grade tumors has significantly increased over time, documented in cases reported from the Urological Clinic, Belgrade, in the period 1971—1985 and later in 1986—1998.

References

1. Nikolic, J. Epidemic nephropathy and upper urothelial tumors. Izdavacko preduzece Beograd A.D. Belgrade, 2006
2. Petronic, V. “Tumors of the upper urothelium and endemic nephropathy” in Endemic Nephropathy, ed by Radiovanovic, Z, Sindic, M., Polenakovic, M., Dukonivic, L, Petronic, V. Zavod za Udzenike I Nasravna Sredstfva, Beograd, 2000.
3. Nikolic, J., Djokic, M., Crnomarkovic, D., Marinkovic, J Upper urothelial tumors and Balkan Nephropathy Responsible Diseases Facta Universitatis 9 (1) pp 113-118 (2002)
4. Nikolic, J., Djokic, M., Ignjatovic, I, Stefanovic, V. Upper urothelial tumors in emigrants from Balkan endemic nephropathy areas in Serbia (*study of 1121 patients with documented UUT*) Urol Int 77: 240-244 (2006).
5. Grollman, A et al, Aristolochic acid and the etiology of Balkan endemic nephropathy Proc Nat Acad Sci., 104: 12129-12134 (2007) (*ref 69 in the NTP draft report*)